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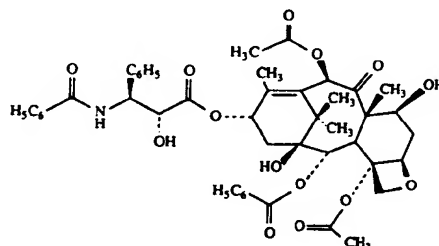
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Supercritical extraction of taxanes.

A method for extracting taxanes such as taxol, comprising the use of supercritical fluids.

The instant invention relates to a method for extracting taxanes from mixtures containing such compounds, and particularly for extracting taxanes from plant or plant-derived materials. The taxanes extracted may be used as pharmaceuticals, or may be used as intermediates in the preparation of pharmacologically active taxanes.

Taxanes are diterpene compounds which find utility in the pharmaceutical field. For example, taxol, a taxane having the structure:



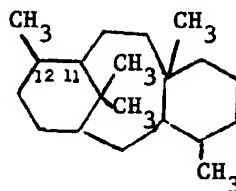
has been found to be an effective anticancer agent, particularly useful in the treatment of ovarian cancer. Cephalomannine, also a taxane, has been reported as a chemotherapeutic agent for the remission of leukemia in U.S. Patent no. 4,206,221.

Taxanes such as those above may be found in plant materials, and have been isolated therefrom. For example, the extraction of taxol from trees of the *Taxus* genus using liquid methanol has been reported. However, taxanes are generally present in plant materials in relatively small amounts so that, in the case of taxol, for example, large numbers of the slow-growing yew trees forming a source for the compound may be destroyed. Further, large amounts of organic solvents may be employed in a conventional liquid extraction, which may be time consuming as well. Thus, the art has continued to search for ever more efficient and environmentally safe methods for obtaining taxanes which minimize the use of plant materials and organic solvents.

The instant invention provides a method for extracting a taxane from a mixture containing such taxane and, particularly, for extracting a taxane from a plant or plant-derived material, comprising the step of contacting the mixture with a supercritical fluid capable of solubilizing at least part of the taxane contained therein.

The instant invention provides an efficient method for obtaining taxanes from mixtures with other compounds or materials, and is especially useful in separating taxol, a potent anticancer agent, from trees of the *Taxus* genus.

Taxanes are diterpene compounds containing the taxane carbon skeleton:



which skeleton may contain ethylenic unsaturation in the ring system thereof. The extraction of any taxane from a mixture containing such taxane is contemplated within the scope of the instant invention. It is of particular interest to separate taxanes having the above carbon skeleton wherein the 11,12-positions are bonded through an ethylenic linkage. Such taxanes include taxol, cephalomannine, baccatin III, 10-deacetyl baccatin III, and 10-deacetyl cephalomannine. The term "taxane", as used in this specification, includes salts as well as solvates, of taxane compounds. Extraction of taxol is a particularly preferred embodiment of the instant invention.

The term "extraction", as used in this specification, encompasses isolation and/or purification of a taxane compound. Any mixture containing one or more taxanes in admixture with other compounds or materials may be employed in the method of the instant invention. Extraction of a single taxane, or simultaneous extraction of two or more taxanes, may be achieved according to instant method.

A preferred embodiment of the instant method relates to the separation of one or more taxanes from plant or plant-derived materials. Exemplary plant materials containing taxanes which may be employed include plants of the genera *Amentotaxus*, *Austrotaxus*, *Cephalotaxus*, *Pseudotaxus*, *Taxus* and *Torreya*. Preferred plant materials are trees of the genus *Taxus* such as *T. brevifolia*, *T. baccata*, *T. media*, *T. wallichiana*, *T. canadensis* and, especially, *T. cuspidata*.

Any part of the plant containing one or more taxanes may be employed such as the bark, roots, leaves or needles, branches, twigs, wood, seeds or whole seedlings. Preferably, prior to contact with the supercritical fluid, the plant material is first ground to a suitable particle size. Grinding of the plant material may be achieved by conventional means such as through use of a chipper and/or a grinding mill.

Materials derived from the aforementioned plant materials may also be employed in the method of the instant invention. The term "plant-derived material", as used in this specification, denotes any material which is obtained from a plant source and which contains one or more taxanes in admixture with other compounds. Thus, for example, an initial extraction of a plant source containing taxane may be conducted by a method such as liquid extraction, and the crude extract so obtained treated by the supercritical extraction method of the instant invention to separate a taxane therefrom.

The term "supercritical fluid" denotes fluids which are above both their critical temperature (T_c) and critical pressure (P_c), and includes both single fluids and fluid mixtures. The skilled artisan may determine whether a fluid is supercritical, that is, is at or above a temperature at which it cannot be liquified by pressure. The supercritical fluid employed in the instant invention is of a nature and quantity so as to be capable of selectively solubilizing at least part of the taxane contained in the mixture contacted. Particularly at higher pressures, use of a higher density of supercritical fluid may provide enhanced extraction. Conditions within the supercritical region are preferably selected so that decomposition of the taxane or taxanes to be extracted is minimized or completely avoided.

Exemplary supercritical fluids which may be employed include, either alone or in admixture with each other or a modifier as appropriate, nitrous oxide (N_2O), ammonia (NH_3), alkanes such as n-butane and n-pentane, sulfur hexafluoride (SF_6), inert gases such as Xe, haloalkanes, particularly fluoroalkanes or chlorofluoroalkanes such as CCl_2F_2 and CHF_3 , and freon compounds, and, most preferably, carbon dioxide (CO_2) which is desirable from a safety and environmental standpoint. The term "modifier", as used in this specification, denotes any compound which, when employed in the instant method, enhances the ability of the supercritical fluid to selectively extract one or more taxanes from the mixture contacted. For example, when plant materials are employed in the instant method, the modifier may penetrate the cell wall of the plant material and facilitate contact between the supercritical fluid and taxane.

Exemplary modifiers are compounds which are solvents for the taxane to be separated, preferably good solvents in which the taxane to be separated is highly soluble. Preferred modifiers include organic solvents such as alkanols, for example, methanol, ethanol and isopropanol; aromatic hydrocarbons, for example, toluene; esters, for example, ethyl acetate; chloroalkanes, for example, chloroform ($CHCl_3$) and methylene chloride; ketones, for example, acetone; propylene carbonate; and acetonitrile. Acetone and acetonitrile are particularly preferred. Where a pharmaceutical utility for the taxane or taxanes to be extracted is contemplated, use of a pharmaceutically acceptable modifier is desirable. Acetone is preferred in the latter case.

The modifier may be contacted with the mixture, such as a plant or plant-derived material, prior to contact with the supercritical fluid and/or may be contacted with the mixture as part of the supercritical fluid. For example, in the latter case, the modifier may be pre-mixed so as to form part of the supercritical fluid.

A preferred embodiment of the instant method is that where a plant or plant-derived material is pre-contacted with the modifier, such as by presoaking the former with liquid modifier prior to contacting the mixture so formed with supercritical fluid. The plant or plant-derived material may be further wetted with liquid modifier, subsequent to pre-soaking and prior to contact with the supercritical fluid. Pre-soaking may be conducted for a time period as short as a few seconds, that is, providing almost instantaneous contact of the mixture with modifier and supercritical fluid, or longer if desired. Preferred times for pre-soaking are from about 1 to 5 seconds to about 1 hour.

Preferred amounts of modifier are those where the weight percent of modifier, based on the weight of fluid such as CO_2 , is from a trace percent, for example 0.001% or less, to about 15%. It is desirable that the amount of modifier does not exceed that at which supercritical conditions may be attained at a temperature and pressure suitable from a practical standpoint.

The amount of supercritical fluid employed is a function of the type of fluid, the temperature and pressure above supercritical, the extraction equipment used, and the amount of taxane to be extracted. In general, longer contact times between supercritical fluid and the mixture containing taxane will provide enhanced recovery.

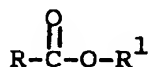
The terms "alkane" and "alkyl", as used herein, preferably denote compounds or groups having straight or branched aliphatic hydrocarbon chains of from 1 to 12 carbons.

The term "haloalkane", as used herein, preferably denotes alkanes as described above substituted with one or more halogen atoms selected from chlorine, fluorine, bromine and iodine. The term "chloroalkane", as used herein, preferably refers to such compounds which are substituted by one or more chlorine atoms.

The term "alkanol", as used herein, preferably denotes alkanes as described above, substituted with one or more hydroxyl groups.

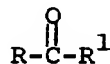
The terms "aromatic hydrocarbon" and "aromatic hydrocarbyl", as used herein, preferably denote compounds or groups having an aromatic ring system of from 6 to 12 carbon atoms, optionally substituted with one or more alkane groups as described above.

The term "ester", as used herein, preferably denotes compounds of the formula



where R and R¹ are independently selected from alkyl and aromatic hydrocarbyl groups as described above.

The term "ketone", as used herein, preferably denotes compounds of the formula



where R and R¹ are as described above.

The method of the instant invention may be conducted in a continuous, semi-batch or batch mode.

A particularly preferred embodiment of the instant invention is that where taxol is extracted from a mixture, preferably from a plant or plant-derived material, using a supercritical fluid and a modifier. Preferably, the supercritical fluid is carbon dioxide and the modifier is acetone or acetonitrile. It is preferred to employ carbon dioxide at pressures greater than about 72.9 atm, more preferably from about 300 to about 700 atm, particularly from about 400 to about 500 atm, and temperatures greater than about 31.3°C, more preferably from about 32°C to 55°C, particularly from about 35°C to about 45°C.

Subsequent to contact with the mixture, such as the plant or plant-derived material, the supercritical fluid will contain a quantity of taxane. The supercritical fluid containing taxane may then be separated from the mixture. Separation of the taxane from the supercritical fluid may be achieved by lowering the pressure and/or the temperature of the fluid to a subcritical condition at which the taxane is less soluble. The supercritical fluid containing taxane may be depressurized in one or more stages, where, when more than one stage is employed, the subsequent stage is at a lower pressure than the preceding stage. Preferably, the supercritical fluid containing taxane is depressurized into an open chamber or into a liquid solvent maintained at subcritical pressure and temperature, most preferably atmospheric pressure and room temperature. As the supercritical fluid containing taxane enters the chamber or solvent, the fluid equilibrates to or approaches the subcritical conditions at which the chamber or liquid solvent is kept, and, in the former case, the taxane is deposited, while in the latter case the taxane is taken up, by dissolution, into the liquid solvent. The subcritical conditions are preferably selected so that the fluid, originally supercritical, becomes a gas which separates off, for example, from the liquid solvent containing dissolved taxane.

Further purification of the taxane obtained may be achieved, if desired, by the use of one or more additional stages of supercritical extraction according to the instant method. Conventional methods of purification may also be employed, such as high pressure liquid chromatography, thin layer chromatography, column chromatography or liquid extraction. Supercritical fluid chromatography (SFC) may also be employed. Additional purification may be used, for example, to separate one taxane from another when two or more taxanes have been extracted from a mixture containing other compounds or materials according to the instant invention. Preferably, the taxane is ultimately obtained in substantially pure form.

As discussed above, taxanes are compounds which find utility in the pharmaceutical field, particularly as anticancer agents. Taxol is exemplary of the pharmacologically active taxanes which also include, for example, cephalomannine. The pharmacologically active taxanes may be used to treat patients suffering from cancers such as ovarian cancer, melanoma, breast, colon or lung cancer, and leukemia. Other pharmacologically active compounds which may be obtained by the method of the invention are taxanes bearing a xylose unit at C-7, such as those described in Senilh et al., *Journal of natural Products*, Vol. 47, no. 1, pp. 131 - 137 (Jan. - Feb. 1984).

The term "patients", as used herein, preferably refers to mammals such as dogs, cats, and other domestic animals and, most preferably, refers to humans. Pharmacologically active taxanes may be administered by means selected by the skilled artisan such as oral or parenteral means, and in effective dosages which may also be selected according to methods known to the skilled artisan. Effective dosages are those which allow mitigation or cure of the malady for which treatment is sought, such as dosages which maintain or decrease the size of a tumor. Generally, an effective dose is in the range of about 0.5 to about 5.0 mg/kg of body weight per day. The pharmacologically active taxane may be employed alone, or in conjunction with other compounds

effective for treatment and/or inert substances such as pharmaceutically acceptable diluents or carriers.

Taxanes obtained by the method of the instant invention may also be used as intermediates to prepare other, pharmacologically active taxanes, the latter which may be used as described above. The method of the instant invention may thus facilitate preparation of such pharmacologically active taxanes by providing an efficient means for obtaining the taxane starting material.

Exemplary taxanes which may be obtained by the method of the instant invention and which may be used as intermediates in the preparation of pharmacologically active taxanes include cephalomannine, baccatin III, 10-deacetyl baccatin III, and 10-deacetyl cephalomannine. Methods known to the skilled artisan may be employed to convert the taxane intermediate to the pharmacologically active taxane desired. For example, Denis et al., *J. Am. Chem. Soc.*, **110**, 5917 - 5919 (1988) describes a method for converting 10-deacetyl baccatin III to taxol. Reductive cleavage of the C-13 side chain, for example, allowing the conversion of cephalomannine to taxol, is described by Magri et al., *J. Org. Chem.*, Vol. 51, no. 16, 3239 - 3242 (1986). The taxane to be converted may be inactive, although conversion of one active taxane to another taxane, the latter of which is effective for treatment of a different malady, or possesses greater potency than the starting material, is contemplated.

The following examples are provided to illustrate the method of the invention, and are not intended to limit the scope of the instant claims.

Example

Supercritical Extraction of Taxol from *Taxus cuspidata*

A. Extraction Apparatus

Figure 1 illustrates the arrangement of the components used for the following extractions. Liquid carbon dioxide was pressurized by the pump/controller (1) (Suprex SFE-50 Microextractor with a syringe pump from Suprex Corp.). Opening the outlet valve on the pump sent the supercritical carbon dioxide to the extraction vessel (2) (stainless steel HPLC guard column (21.2 mm x 100 mm) rated to 6000 psi with stainless steel frits and access to either end of the column). The extraction vessel was maintained at a constant temperature in an oven (3). In the oven, the liquid carbon dioxide was above its critical temperature and critical pressure, and thus was maintained in the supercritical state. A six-way valve (4) controlled and directed the supercritical carbon dioxide from the extraction vessel. When the valve switch (5) was in the *inject* mode, the supercritical fluid filled the extraction vessel for a static extraction. When the valve was switched to the *load* mode, the supercritical fluid was released to the restrictor (a 30-cm length of 0.020 inch i.d. stainless steel tubing, crimped on the very tip to restrict carbon dioxide flow) for a dynamic extraction. The restrictor tip (6) was immersed in the fluid contained in the collector (7) (a 1-liter HPLC solvent reservoir).

The restrictor was employed to maintain high pressures within the extraction vessel while venting the supercritical fluid out of the system. Extraction of plant material may plug the small inner diameter of commercially available restrictors. To produce a reproducible restrictor for maintenance of high back pressures, with a minimum of plugging, a modification was made to the commercially available restrictor design.

A 20 mm length of 5 μ m stainless steel tubing was smoothly cut with a tubing cutter. The tubing was fitted with a stainless steel ferrule which was tightened to the tubing with a female adaptor. A male union was placed on the restrictor and the end opposite of the ferrule crushed with a large table vise that evenly crimped the very end of the tip (2 mm).

The tip of the restrictor was adjusted as follows. To the end of a length of 20 μ m stainless steel tubing, the male fitting was attached and joined with a double female union that was drilled out to 20 μ m internal diameter. The restrictor was attached to the union and the tip was connected to a digital bubble flow meter. The flow was monitored through the restrictor at an operating pressure of 430 atm. The wide part of the crimp was opened as needed with a pair of pliers to maintain a flow rate fast enough to flush out the compounds of interest, but slow enough that there was no aerosol formation that could lead to compound loss. A restrictor flow of 400 ml/min was employed to accomplish this.

B. Extraction Procedure

Milled plant material (*Taxus cuspidata*, 10 \pm 0.1 g) was weighed out into a plastic weighing boat. With a graduated cylinder, 10 ml acetonitrile was measured out and distributed over the plant material, and mixed well with a spatula. The weighing boat was covered to avoid evaporation of the acetonitrile. The sample was allowed to soak for 20 minutes.

A small piece of silanized glass wool was placed into, and was pushed to the bottom of, the extraction vessel. Enough glass wool was used to obtain a depth of approximately 1 cm.

With a powder funnel, the extraction vessel was filled with the soaked material, and packed with a glass rod. When all of the material had been transferred into the extraction vessel, an additional 5 ml of acetonitrile were added to the sample in the vessel. The material filled the extraction vessel such that there was about 2 cm of free space above the sample. This void was filled with another plug of glass wool (approximately 2 cm thick).

Static Extraction

The pump was brought to operating pressure, and the outlet valve opened to fill the extraction vessel with supercritical carbon dioxide. Conditions at this point were such that liquid carbon dioxide was present in the extraction vessel. The system was allowed to equilibrate to the supercritical operating pressure and temperature set forth in Table I. Once the set temperature and pressure were attained, timing of the static extraction was begun. The density report displayed by the controller monitor was observed.

Dynamic Extraction

After 30 minutes of static extraction, the valve was switched to deliver the supercritical fluid to the collector. The collector contained 50 ml of acetonitrile into which the restrictor tip was submerged about 1.5 - 2.0 inches. The timer was set for another 30 minutes, during which bubbling at the tip of the restrictor was observed. After 30 minutes, the valve was again switched, and the restrictor allowed to depressurize. The acetonitrile in the collector was deep green in color at this time.

Sample Collection

The contents of the collector were transferred into two 50 ml tubes. The collector was washed with 5 ml acetonitrile which was combined with the contents of the tubes. The sample volume was reduced to dryness by rotary evaporation, and the amount of the residue was weighed. The residue was reconstituted in 1.0 ml acetonitrile. This extracted taxol solution was maintained at -20°C until analysis by HPLC.

C. Results

Duplicate extractions were made under each set of the conditions listed in Table I to check the extraction reproducibility. Table II shows the amounts of taxol extracted, under the various conditions of temperature and pressure.

Figure 2 illustrates the relation of the amount of taxol extracted to the density at two pressures. Extraction at a high pressure and a low temperature provides the highest density and, at 430 atm, the highest taxol recovery. A temperature of 35°C and a pressure of 430 atm were the best conditions for this extraction within the temperature and pressure ranges examined. Figure 3 illustrates the relation of the amount of taxol extracted to the temperature. Figure 4 shows the increased influence of density on the recovery of taxol as the set temperature is decreased.

Extractions of milled plant material without acetonitrile wetting gave no detectable amounts of taxol. Modification of supercritical carbon dioxide was thus employed.

TABLE I
EXTRACTION CONDITIONS

Temperature (°C)	Pressure (atm)
35	330
45	330
55	330
35	430
45	430
55	430

TABLE II

Sample	µg Taxol Extracted*	Temperature (°C)	Pressure (atm)	Density (g/mL)
RA-I	238	35	330	0.945
RA-II	197	35	330	0.948
RA-III	222	35	330	0.947
RA-IV	367	35	330	0.946
RB-I	603	45	330	0.911
RB-II	654	45	330	0.911
RC-I	684	55	330	0.872
RC-II	751	55	330	0.872
RD-I	969	35	430	0.985
RD-II	883	35	430	0.987
RE-I	790	45	430	0.955
RE-II	625	45	430	0.955
RE-III	555	45	430	0.955
RF-I	655	55	430	0.923
RF-II	710	55	430	0.923
RF-III	510	55	430	0.923

Example 2Supercritical Extraction of Taxol from *Taxus cuspidata*: Use of Higher Pressure

5 The extraction procedure of Example 1 was followed, with the exception that a pressure of 680 atm, and a temperature as indicated in Table III, was employed, and the apparatus used was a Model 703 Dionex supercritical extractor. Taxol was extracted in amounts also shown in Table III.

10 Table III

15	<u>Sample</u>	<u>µg Taxol extracted per 10 g plant material</u>	<u>Temp(°C)</u>	<u>Density (g/ml)</u>
	DX1	320	35	1.086
20	DX2	500	35	1.086
	DX3	380	35	1.086
	DX4	580	35	1.086
25	DX5	680	45	1.065

Example 3 Supercritical Extraction of Taxol from *Taxus cuspidata*: Methanol as Modifier

30 The extraction procedure of Example 1 was followed, with the exception that methanol was employed in place of acetonitrile as the modifier. The temperature and pressure employed, and the amount of taxol extracted, is shown in Table IV.

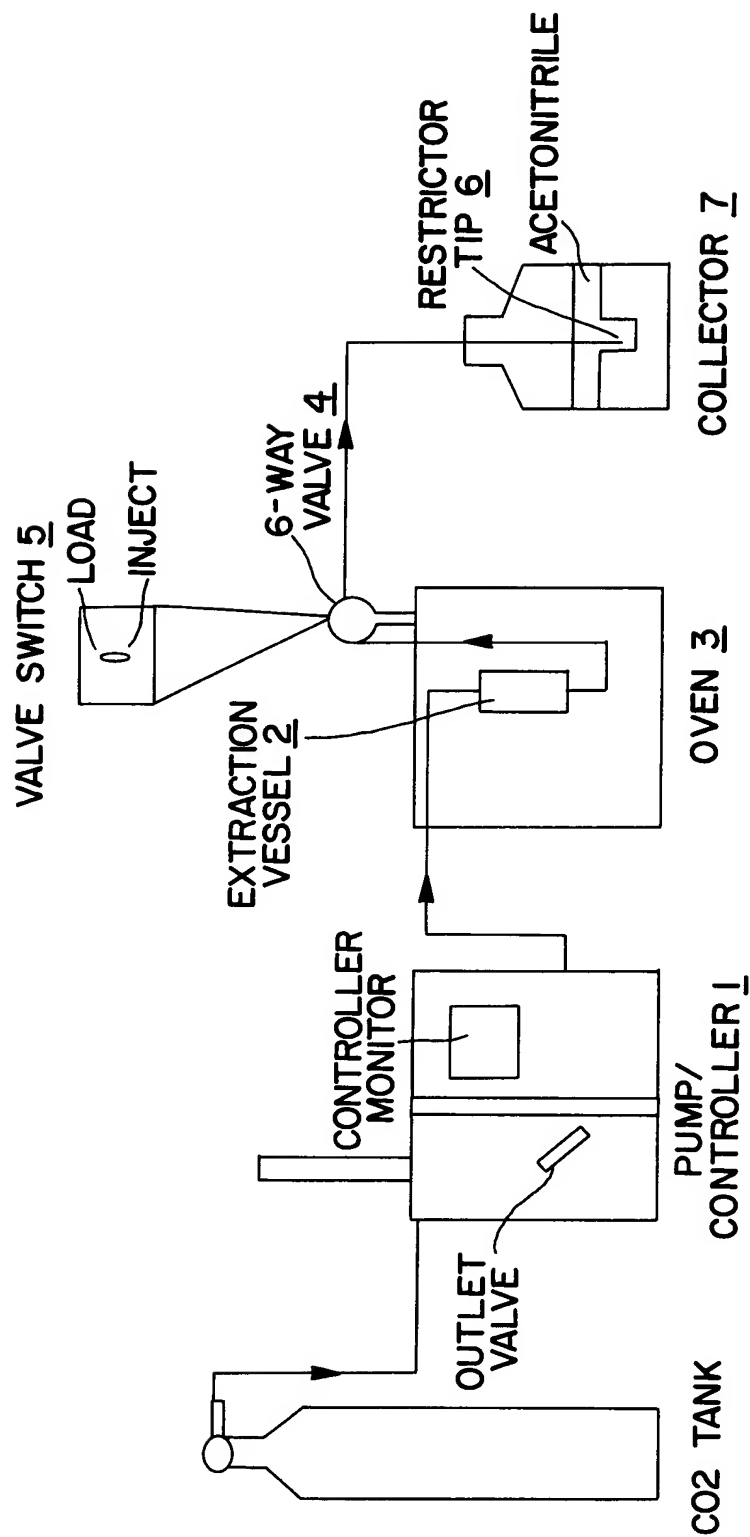
35	<u>Sample</u>	<u>µg Taxol extracted per 10 g plant material</u>	<u>Temp(°C)</u>	<u>Pressure (atm)</u>	<u>Density (g/ml)</u>
	RG-II	350	45	330	0.911
	RG-III	60	45	330	0.908
	RH-I	30	35	430	0.987
45	RH-II	240	35	430	0.987
	RH-III	162	35	430	0.987
	RJ-IA	240	35	430	0.987
50	RK-I	420	45	430	0.954
	RK-II	210	45	430	0.954
	RL-I	420	55	430	0.923

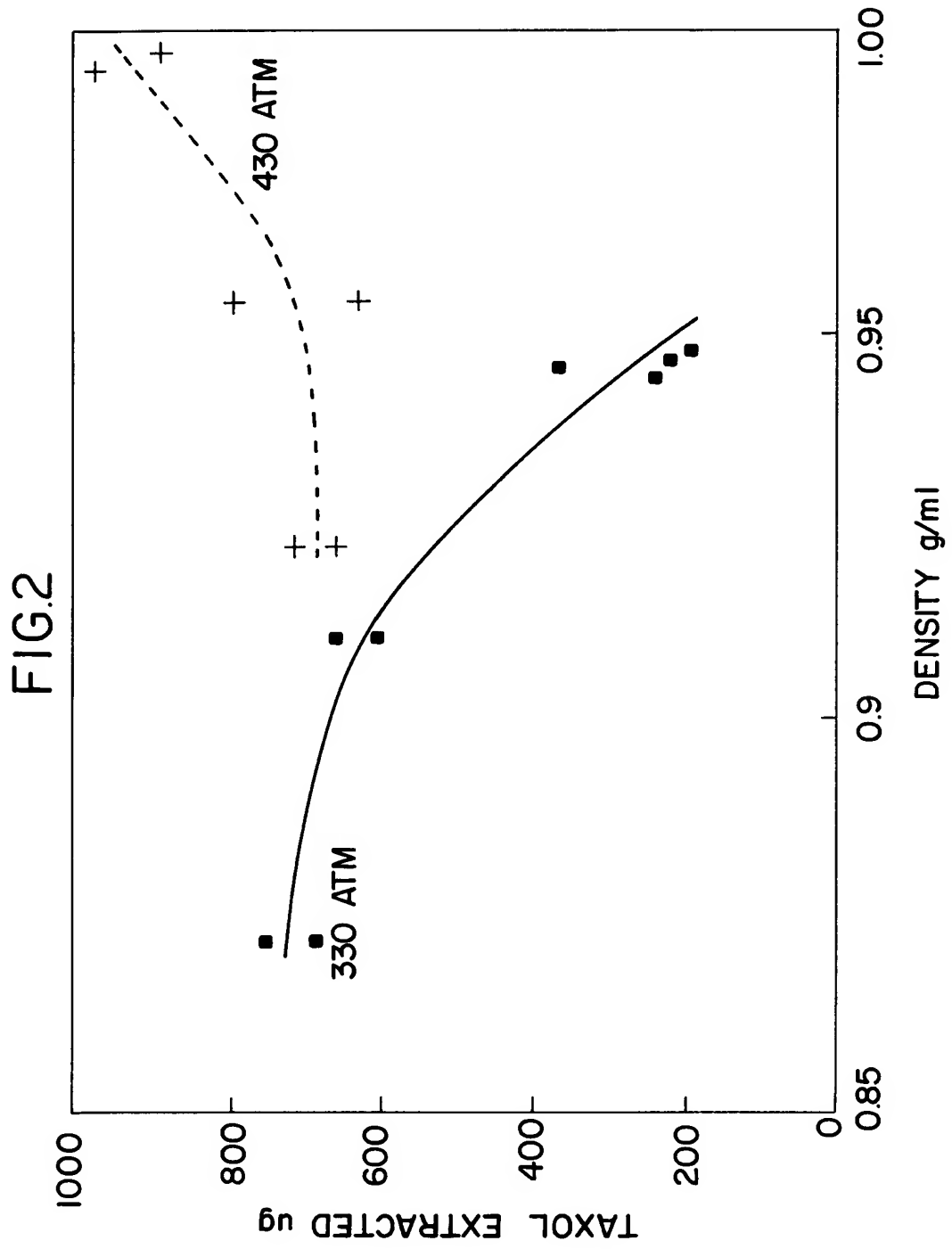
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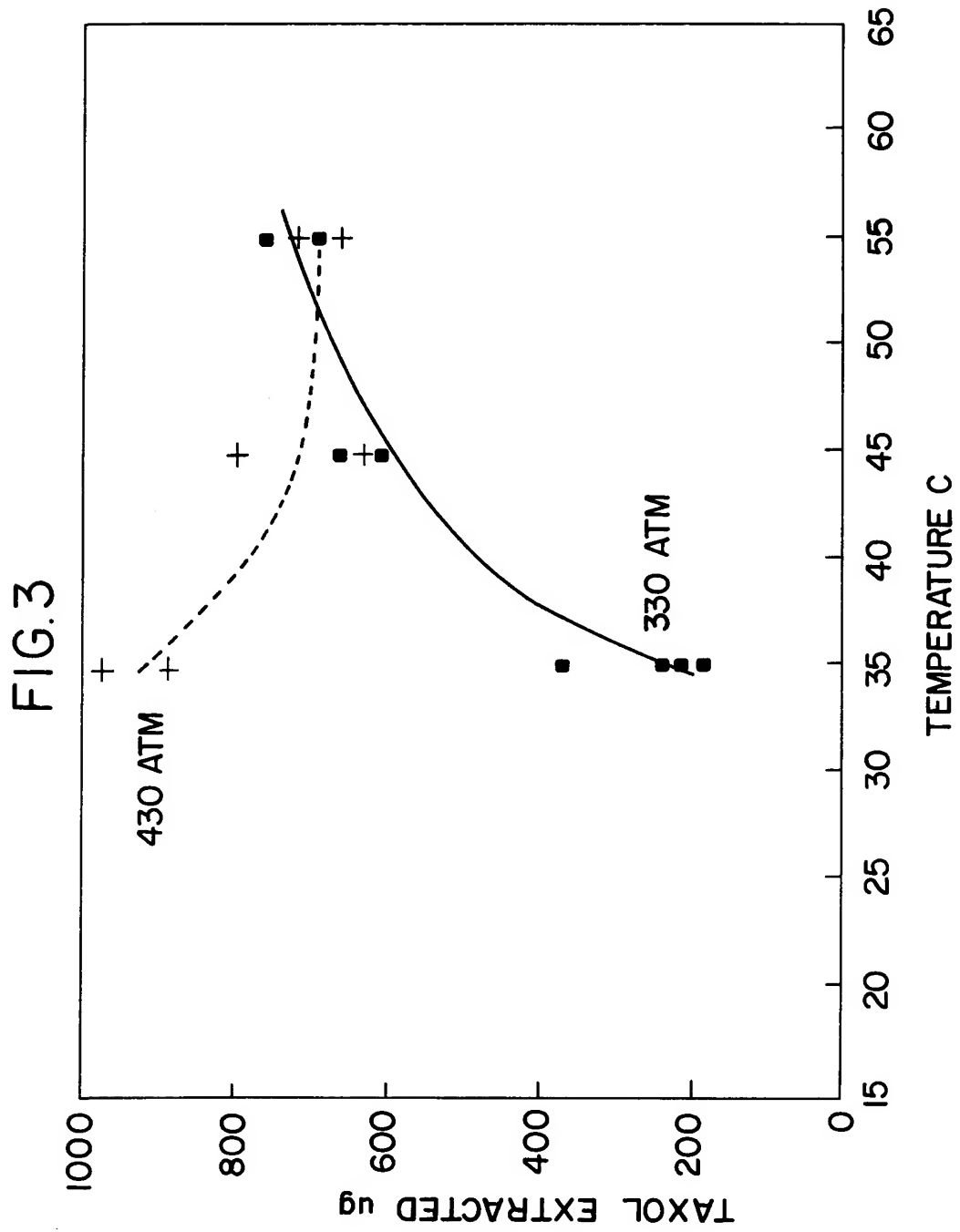
Claims

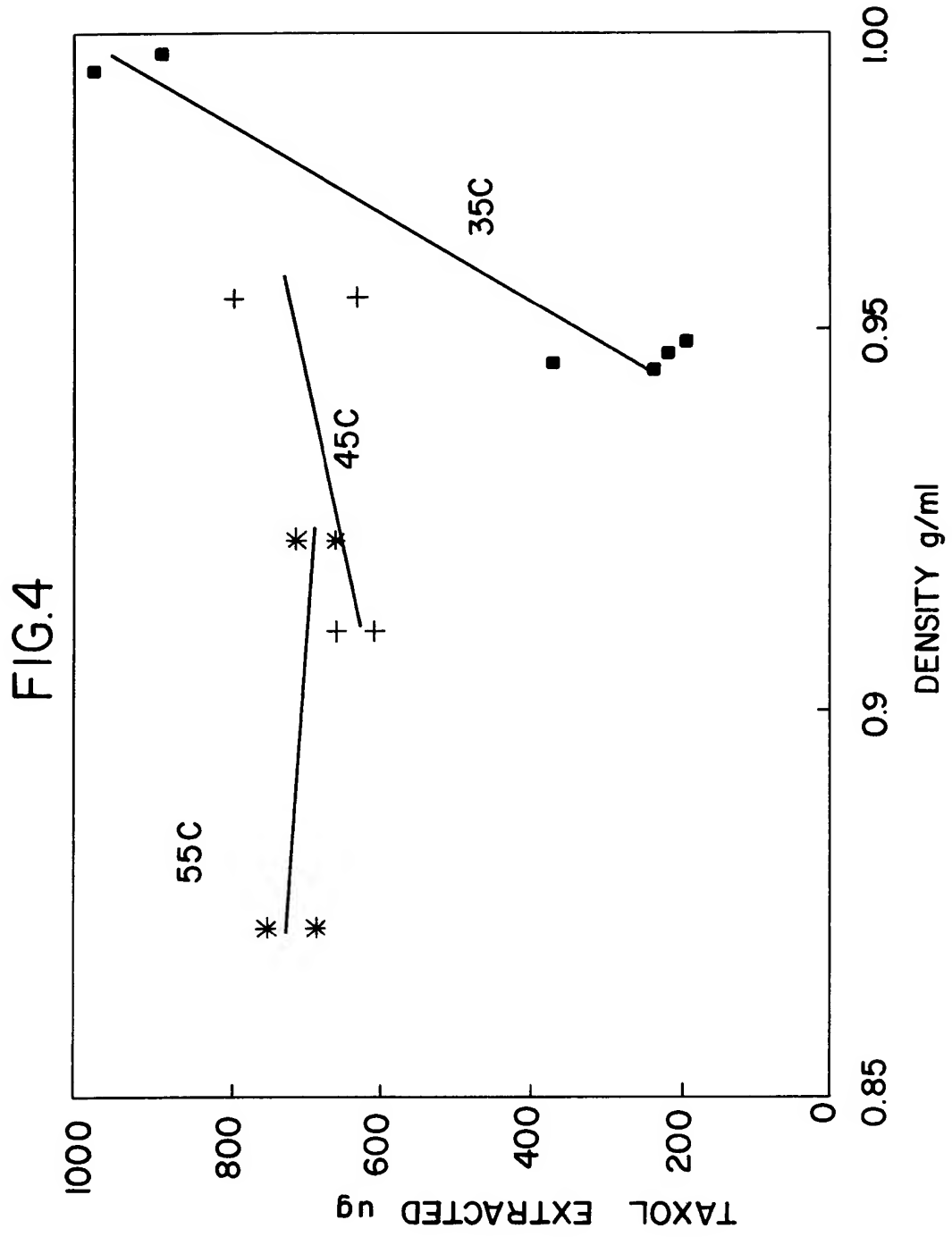
1. A method for extracting a taxane from a mixture containing said taxane, comprising the step of contacting the mixture with a supercritical fluid capable of solubilizing at least part of the taxane contained therein.
- 5 2. The method of claim 1, wherein one or more taxanes selected from taxol, cephalomannine, baccatin III, 10-deacetylbaccatin III, or 10-deacetylcephalomannine are extracted.
3. The method of claim 2, wherein taxol is extracted.
- 10 4. The method of any preceding claim, wherein said mixture is a plant or plant-derived material.
5. The method of claim 4, wherein said plant material is selected from a plant of the genus *Amentotaxus*, *Austrotaxus*, *Cephalotaxus*, *Pseudotaxus*, *Taxus*, or *Torreya*.
- 15 6. The method of claim 5, wherein said plant material is from a tree of the *Taxus* genus.
7. The method of claim 6, wherein said tree is selected from *T. brevifolia*, *T. baccata*, *T. media*, *T. wallichiana*, *T. canadensis* or *T. cuspidata*.
- 20 8. The method of claim 5, 6 or 7, wherein said plant material includes one or more parts of the plant selected from the bark, roots, leaves or needles, branches, twigs, wood, seeds or whole seedlings.
9. The method of any preceding claim, wherein said supercritical fluid includes, either alone or in admixture with each other or a modifier, nitrous oxide, ammonia, an alkane, sulfur hexafluoride, an inert gas, a haloalkane, or carbon dioxide.
- 25 10. The method of claim 9, wherein said supercritical fluid is carbon dioxide admixed with a modifier.
11. The method of claim 10, wherein said modifier is an organic solvent for the taxane to be extracted.
- 30 12. The method of claim 11, wherein said modifier is an alkanol, an aromatic hydrocarbon, an ester, a chloroalkane, a ketone, propylene carbonate or acetonitrile.
13. The method of claim 12, wherein said modifier is acetone or acetonitrile.
- 35 14. The method of any one of claims 10-13, wherein said modifier is pre-contacted with a plant or plant-derived material in liquid form and then, subsequently, the mixture so formed is contacted with supercritical carbon dioxide.
15. The method of any one of claims 10-14, wherein the pressure of the carbon dioxide employed is greater than about 72.9 atm.
- 40 16. The method of claim 15, wherein the pressure of the carbon dioxide employed is from about 400 to about 500 atm.
17. The method of any one of claims 10-16, wherein the temperature of the carbon dioxide employed is greater than about 31.3°C.
- 45 18. The method of claim 17, wherein the temperature of the carbon dioxide employed is from about 35°C to about 45°C.
- 50 19. The method of any preceding claim, wherein, subsequent to contact with said mixture, the supercritical fluid containing taxane is separated therefrom.
20. The method of claim 19, wherein the supercritical fluid containing taxane is depressurized into an open chamber or into a liquid solvent for said taxane.

FIG.1











European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 5953

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 93, no. 9, 5 May 1971, Washington, DC, US, pages 2325 - 2327; M.C. WANI ET AL.: 'Plant tumour agents. VI. The isolation and structure of taxol, a novel antileukaemic and antitumour agent from <i>Taxus brevifolia</i> ' * page 2325 *	1	C07D305/14 B01D11/04
D,A	US-A-4 206 221 (R.W. MILLER et al.) * column 2 - column 4 *	1	
A	US-A-4 964 995 (H.L. CHUM et al.) * claim 1 *	1	
P,X	CHEMICAL ABSTRACTS, vol. 116, no. 26, 29 June 1992, Columbus, Ohio, US; abstract no. 262349E, D.W. JENNINGS et al. 'Supercritical extraction of taxol from the bark of <i>Taxus brevifolia</i> ' page 446 ; & JOURNAL OF SUPERCRITICAL FLUIDS, 1992, 5(1), 1-6	1-12,15, 17,18	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D B01D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11 SEPTEMBER 1992	Examiner RUSSELL F. ENGLISH
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			

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